SUPPLEMENT ARTICLE

Risk of Sequelae after *Chlamydia trachomatis* Genital Infection in Women

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***Chlamydia trachomatis* infection, the most common reportable disease in the United States, can lead to pelvic inflammatory disease (PID), infertility, ectopic pregnancy, and chronic pelvic pain. Although *C. trachomatis* is identified among many women who receive a diagnosis of PID, the incidence and timing of PID and long-term sequelae from an untreated chlamydial infection have not been fully determined. This article examines evidence reviewed as part of the Centers for Disease Control and Prevention Chlamydia Immunology and Control Expert Advisory Meeting; 24 reports were included. We found no prospective studies directly assessing risk of long-term reproductive sequelae, such as infertility, after untreated *C. trachomatis* infection. Several studies assessed PID diagnosis after untreated chlamydial infection, but rates varied widely, making it difficult to determine an overall estimate. In high-risk settings, 2%–5% of untreated women developed PID within the ~2-week period between testing positive for *C. trachomatis* and returning for treatment. However, the rate of PID progression in the general, asymptomatic population followed up for longer periods appeared to be low. According to the largest studies, after symptomatic PID of any cause has occurred, up to 18% of women may develop infertility. In several studies, repeated chlamydial infection was associated with PID and other reproductive sequelae, although it was difficult to determine whether the risk per infection increased with each recurrent episode. The present review critically evaluates this body of literature and suggests future research directions. Specifically, prospective studies assessing rates of symptomatic PID, subclinical tubal damage, and long-term reproductive sequelae after *C. trachomatis* infection; better tools to measure PID and tubal damage; and studies on the natural history of repeated chlamydial infections are needed.**

Genital infection with *Chlamydia trachomatis*, the most common reportable disease in the United States [1], can lead to serious sequelae among women, including pelvic inflammatory disease (PID), tubal factor infertility, ectopic pregnancy, and chronic pelvic pain [2–7]. Approximately 8% of US women and 15% of Swedish women have reported a PID diagnosis in their lifetimes [8–10]. PID is thought to occur as microorganisms ascend from the lower genital tract, infecting and causing inflammation of the uterus, fallopian tubes, and ovaries [11]. Although the microbial etiology of PID is not fully delineated, *C. trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium,* and microorganisms associated with bacterial vaginosis are frequently isolated from the lower and upper genital tracts of women with PID [12–17]. Although *C. trachomatis* is among the most frequent pathogens associated with symptomatic PID [15, 18, 19], isolated in the upper genital tract of up to a quarter of these patients [12, 18, 20], it has also been associated with a wide spectrum of upper genital tract pathology ranging from asymptomatic endometritis [21–25] to symptomatic, laparoscopically confirmed salpingitis [18]. This highlights the importance of this pathogen in the etiology of both acute PID and subclinical upper tract disease. The reproductive and gynecologic consequences of PID, including infertility [2, 7, 26, 27], ectopic pregnancy [2, 7, 26,

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28], recurrent PID [26, 28], and chronic pelvic pain [26–29], can result from damage to the cilia lining the fallopian tubes, fallopian tube blockage or closure, or adhesion formation among pelvic organs.

Because of the potential for *C. trachomatis* infection to cause serious sequelae, chlamydia screening and treatment programs have been implemented in many countries to shorten the duration of infection, prevent tubal damage among those infected, and reduce *C. trachomatis* transmission. However, recent surveillance data in several countries, including the United States, suggest that chlamydia rates have not been decreasing, despite ongoing control efforts [30, 31]. This has raised several fundamental questions about the natural history of *C. trachomatis* infection [32]. For example, if *C. trachomatis* infections were not detected and treated through a control program, what proportion would result in sequelae? This influences the overall potential benefit of the program and its cost-effectiveness. An even more important consideration may be the timing of tubal inflammation and damage relative to acquisition of infection. This timing affects the likelihood that infections can be detected and treated by a control program before development of symptomatic PID or development of tubal damage that could ultimately lead to infertility or ectopic pregnancy. Contributing to observed increases in chlamydia case rates is likely an increase in repeat infections, which are common in some populations [33]. Thus, another fundamental question is how harmful repeated *C. trachomatis* infections are in leading to sequelae. This review was developed to address these key questions, which were raised at the April 2008 Chlamydia Immunology and Control Expert Advisory Meeting sponsored by the Centers for Disease Control and Prevention (CDC). This article critically examines evidence addressing the risk and timing of female reproductive tract sequelae after untreated *C. trachomatis* infection and after repeated chlamydial infection. Gaps in knowledge are identified, and future research needs are proposed.

METHODS

A 3-member committee was composed to systematically identify the literature for review. A search of the literature from 1950 through 2008 was conducted with the Medline computerized database of the US National Library of Medicine. The term "*Chlamydia trachomatis*" was combined with "pelvic inflammatory disease," "salpingitis," "endometritis," "infertility," or "ectopic pregnancy." A separate search was conducted as follows: "pelvic inflammatory disease," "salpingitis," or "endometritis" and "infertility" or "ectopic pregnancy." This yielded a total of 3308 citations. Citations were then limited to human studies involving nonpregnant women, and postabortion and transcervical instrumentation studies were excluded. Additional articles were identified by cross-listing bibliographies of reviewed articles. The selected literature was examined for content, and 24 articles deemed to be most relevant to the key questions were selected for critical review. Six articles examined the prospective risk of PID after untreated chlamydial infection [34–39], and 12 examined risk of long-term reproductive sequelae after PID, including either PID of any cause [7, 15, 27–29, 40] or *C. trachomatis*–associated PID [2, 4, 20, 26, 41, 42]. Two articles prospectively explored the risk of PID after detected and treated chlamydial infection [43, 44], and 6 provided information on the risk of sequelae associated with repeated infection [4, 7, 19, 45–47]. These studies are discussed narratively in the text, and information on study design, population, methods, exposure and outcome measurement, results, strengths, and limitations were tabulated (Tables 1–5).

RESULTS

What is the Risk of Sequelae over Time after an Untreated *C. trachomatis* Infection?

The ultimate objective of chlamydia control programs is to prevent the most serious long-term reproductive consequences of *C. trachomatis* infection—mainly, infertility [48]. However, this outcome may not be recognized for several years after a chlamydial infection has caused tubal damage, because the affected woman may not have tried to become pregnant. In addition, there are ethical and technical limitations in following the natural course of infection, because an infection should be treated promptly once it is detected. Thus, although a number of case-control studies have demonstrated associations between serologic evidence of past chlamydial infection and either tubal factor infertility [5, 49–52] or ectopic pregnancy [3, 53, 54], there are no prospective studies directly evaluating risk of long-term reproductive tract morbidity after untreated *C. trachomatis* infection. PID can serve as a surrogate or intermediary outcome, because its temporal relationship to both chlamydial infection and long-term outcomes is more conducive to study and because it has substantial morbidity and costs [8, 11]. Several studies have attempted to assess the proportion of untreated *C. trachomatis* infections leading to PID [34–39], and another set of studies evaluated the proportion of PID cases leading to infertility and ectopic pregnancy [2, 4, 7, 15, 20, 26–29, 40–42]. Synthesizing these data can offer some insight into the risk of long-term sequelae after untreated chlamydial infection.

PID after untreated chlamydial infection. It is challenging to assess the true incidence of PID among women with untreated *C. trachomatis* infection. Despite this, several studies have described aspects of the natural history of untreated chlamydial infection (Table 1). In 3 investigations involving populations at high risk, occurrence of clinically diagnosed PID in women with untreated chlamydial infection was assessed during the ~14-day interval between testing and treatment. PID occurrence in this interval ranged from 2% to 4.5% among

Table 1. Studies Assessing the Risk of Pelvic Inflammatory Disease (PID) after Untreated *Chlamydia trachomatis* Infection

Reference (year)	No. of women with untreated *C. trachomatis* infection[a]	Population		Methods			Duration of follow-up	Incidence of PID	Validity
		Setting	Symptoms	Design	CT tests used	PID diagnosis			
Stamm et al [39] (1984)	20	STD clinics in Seattle, WA, and Boston, MA (1980s)	Known or suspected uncomplicated *Neisseria gonorrhoeae* infection; *C. trachomatis* prevalence 26% in study population	Prospective cohort of *C. trachomatis*–positive women within RCT of *N. gonorrhoeae* treatment regimens	Culture	Clinical examination	7 weeks	30% (95% CI, 13%-53%; 6 of 20 women) in penicillin plus probenecid arm (ineffectively treated *C. trachomatis*); 2% (1 of 50) among those in other arms (treated more effectively for *C. trachomatis* with trimethoprim-sulfamethoxazole or tetracycline)	Small sample size; generalizability may be limited because of initial coinfection with *N. gonorrhoeae;* timing of *C. trachomatis* acquisition unknown
Rahm et al [38] (1986)	109	Adolescents seeking contraceptives at a counselling bureau in Sweden (1980s)	Healthy, asymptomatic, but *C. trachomatis* prevalence 15.6% in study cohort	Prospective natural history study	Culture	Hospitalized for salpingitis or seen in emergency department for lower abdominal pain/ discharge	12 weeks	3.7% (95% CI, 1.2%–8.6%; 4 of 109 women)	Moderate length of follow-up is a strength; underestimation of PID possible as women not seeking medical care for abdominal pain would be excluded from the definition; timing of *C. trachomatis* acquisition unknown
Hook et al [36] (1994)	93	2 Baltimore STD clinics (1991); predominately young, black, low socioeconomic status	Primarily asymptomatic; excluded women with MPC, PID, or sex partners with STD; *C. trachomatis* test positivity 6.6%	Prospective evaluation of PID occurring between initial screening visit and return for treatment	Culture	Clinical examination	Median 14 days	3.2% (95% CI, 0.8%–8.5%; 3 of 93 women); cases presented 14, 23, and 68 days after initial positive test	Follow-up data available for 74% of *C. trachomatis*–positive women; relatively short length of follow-up; rate of PID in the *C. trachomatis*–negative group unknown; high-risk population; timing of *C. trachomatis* acquisition unknown

Bachmann et al [34] (1999)	67	University of Alabama, Birmingham hospital; mainly emergency department/ walk-in clinic (55%) and gynecology service (31%) (1996)	Almost all symptomatic (91%) but not treated for *C. trachomatis* at initial visit; *C. trachomatis* test positivity at hospital 7.7%	Retrospective cohort study of PID after *C. trachomatis* testing	Culture and EIA	Clinical diagnosis documented in medical chart	Not specified, but assumed short period between testing and return to medical center for treatment	4.5% (95% CI, 1.1%–11.7%; 3 of 67 women)	Relatively small sample size; follow-up data only available on 41% of *C. trachomatis*–positive women; relatively short length of follow-up; rate of PID in the *C. trachomatis*–negative group unknown; high-risk population; overestimation of PID incidence possible as PID may have been present but misdiagnosed in symptomatic women at baseline; timing of *C. trachomatis* acquisition unknown
Morré et al [37] (2002)	30	Low-risk women undergoing screening as part of medical check-up before job engagement, Amsterdam (1995–1997)	Healthy, asymptomatic; *C. trachomatis* prevalence 4%	Prospective natural history study	NAAT; urine specimens every 3 months tested at end of study	Self-reported doctor diagnosis, complaints of lower abdominal pain, or use of *C. trachomatis*–specific antibiotics	1 year	0% (95% CI, 0%–9.5%; 0 of 30 women)	Small sample size; ability to evaluate a longer duration of untreated *C. trachomatis* is a strength; limited by classification of PID by self-report; NAATs may detect infections with lower bacterial burden, perhaps less likely to progress to PID; timing of *C. trachomatis* acquisition unknown
Geisler et al [35] (2008)	115	Birmingham, Alabama, STD clinic (median age, 21 years)	Primarily asymptomatic; *C. trachomatis* prevalence not reported	Prospective evaluation of PID occurring between initial screening visit and return for treatment	Culture (70%) or NAAT (30%)	Clinical examination	Median 13 days	2% (95% CI, 0.3%–5.6%; 2 of 115 women); 1 of the 2 women developing PID acquired a new *N. gonorrhoeae* infection during follow-up; cases presented 7 and 25 days after initial positive test result	Relatively short duration of follow-up; rate of PID in the *C. trachomatis*–negative group unknown; high-risk population; NAATs may detect infections with lower bacterial burden, perhaps less likely to progress to PID; timing of *C. trachomatis* acquisition unknown

NOTE. Data from the Prevention of Pelvic Infection (POPI) trial, an additional study of the risk of PID after untreated *C. trachomatis* infection, were published too late for inclusion in this review but are available elsewhere [70]. CI, confidence interval; EIA, enzyme immunoassay; MPC, mucopurulent cervicitis; NAAT, nucleic acid amplification test; RCT, randomized controlled trial; STD, sexually transmitted disease

[a] Number of women with untreated *C. trachomatis* infection who were evaluated for PID at follow-up.

Table 2. Studies Assessing the Risk of Reproductive and Gynecologic Sequelae after Pelvic Inflammatory Disease (PID) of Any Cause

Reference (year)	Population	Setting	Study design	PID diagnosis	Outcomes	Period	Findings	Strengths	Limitations
Weström et al [7] (1992)	1844 women with laparoscopically confirmed salpingitis and 657 control women with clinically suspected PID but normal laparoscopy findings; inpatients	University Hospital, Lund, Sweden (1960–1984)	Prospective cohort study	Laparoscopy	Infertility (failure to conceive despite regular unprotected intercourse for >1 year); tubal factor infertility verified by HSG, laparoscopy, laparotomy, or combination	Case and control women followed up for 13,400 and 3958 woman-years, respectively	Failure to conceive among subgroup of women trying: 209 (16%) of 1309 case women, 12 (2.7%) of 451 control women; proportion with tubal factor infertility (excluding those with incomplete fertility examinations): 141 (11.1%) of 1262 case women, 0 (0%) of 442 control women; severity of salpingitis on laparoscopy associated with infertility: mild (0.6% tubal factor infertility), severe (21.4% tubal factor infertility); ectopic pregnancy in first pregnancy: 9.1% of case women, 1.4% of control women (P <.001)	Strengths: well done, landmark study with large sample size, laparoscopic confirmation of PID, and HSG identification of tubal factor infertility; control group	May not be generalizable to modern day microbiological and clinical setting; outcome data presented as proportions, so rate of complications over time not known
Stacey et al [27] (1992)	22 women treated for PID	STD clinic or Samaritan Hospital, London, England (1984– 1987)	Prospective study	Laparoscopically confirmed salpingitis	Infertility and chronic pelvic pain evaluated by chart review, clinic examinations, and fertility questionnaires	1–3 years after enrollment	5 (33%) of 15 of women reported difficulty conceiving and 9 (56%) of 16 reported continued pelvic pain after 1 year	Lengthy follow-up and laparoscopic evaluation of PID	Small sample size and loss to follow-up; no control group

Buchan et al [28] (1993)	1200 women hospitalized with first diagnosis of PID and 10,507 control women discharged with other diagnoses	Oxford Record Linkage Study (1970–1985)	Retrospective cohort study	Discharge diagnosis and surgical confirmation (375 cases)	Subsequent hospital admissions for ectopic pregnancy, abdominal pain, endometriosis, hysterectomy, and recurrent PID	Followed up to 15 years	Abdominal pain admissions: 16.7% case women vs 1.7% control women (RR 9.8; 95% CI not presented); ectopic pregnancy: 1.9% case women vs 0.2% control women (RR, 9.5; 95% CI not presented); hysterectomy: 18.2% case women vs 2.3% control women (RR, 7.9; 95% CI not presented)	Large sample size	Women with secondary admission of PID excluded; may not be generalizable to modern setting; women who moved out of area covered by linkage system were missed
Lepine et al [29] (1998)	1288 hospitalized for salpingitis (same population as [7])	Lund, Sweden (1960–1984)	Prospective cohort study	Laparoscopy	Live birth	12 years follow-up	Cumulative live birth rates differed by severity of PID: mild salpingitis (90%), moderate salpingitis (82%), severe salpingitis (57%); compared with women with one case of mild PID, women with severe PID and subsequent diagnoses were more likely not to achieve a live birth (RR, 8.1; 95% CI 3.0–22.2)	Large sample size and laparoscopic confirmation of PID	May not be generalizable to modern microbiological and clinical setting
Ness et al [15] (2002)	831 women enrolled in a RCT of inpatient vs outpatient treatment of mild to moderate PID, recruited from ED, gynecology, STD clinics, and private practice; predominantly black, lower socioeconomic status; one-third reported prior diagnosis of PID	13 US urban clinical sites, 1996–1999 (PEACH study)	RCT	Clinical examination	Interviews every 3–4 months for outcomes of infertility (lack of pregnancy with sex for 12 months with no effective contraception), ectopic pregnancy, chronic pelvic pain (consistent self-reports of pain of at least 6 months duration), recurrent PID (self-report), pregnancy rate, time to pregnancy	Mean 35 months follow-up	No differences in outcomes by treatment arm; cumulative outcomes over ~3 years: infertility (18%), ectopic pregnancy (0.6%), chronic pelvic pain (29%), recurrent PID (14%); pregnancy achieved in 42%; mean time to pregnancy 21 months	Large sample size and lengthy follow-up with active assessment for outcomes; modern-day assessment of multiple outcomes after mild-moderate clinically suspected PID	PID diagnosis by clinical criteria alone and no outcomes among control group reported here (see Haggerty et al [23, 41] in Table 4)

Heinonen and Leinonen [40] (2003)	39 women treated with doxycycline plus metronidazole for salpingitis	Hospital of Tampere, Finland (1983–1988)	Prospective cohort study	Laparoscopy	Questionnaires and hospital chart review for pregnancy, recurrent infections, and infertility	Mean follow-up of 125 ± 44 months	28 women (72%) tried to conceive during the follow-up period: 25 (89%) conceived and 11 (28%) avoided conception; no statistically significant difference ($P = .06$) in cumulative pregnancy rates between mild and severe salpingitis groups; mean time to pregnancy, 38 months; many of these women may have been considered infertile at some point using a standard infertility definition (lack of conception after 12 months of unprotected intercourse), suggests relationship between PID and subfertility	Laparoscopic confirmation of PID and lengthy follow-up for sequelae	Small sample size, self-report of pregnancy, and use of a treatment regimen no longer recommended

NOTE. CI, confidence interval; ED, emergency department; EIA, enzyme immunoassay; HSG, hysterosalpingogram; NAAT, nucleic acid amplification test; RCT, randomized controlled trial; RR, relative risk; STD, sexually transmitted disease.

Table 3. Studies Assessing the Risk of Reproductive and Gynecologic Sequelae after *Chlamydia trachomatis*–Associated Pelvic Inflammatory Disease (PID)

Reference (year)	Population	Setting	Study design	PID diagnosis	Outcomes	Period	Findings	Strengths	Limitations
Brunham et al [2] (1988)	71 women hospitalized for PID	Winnipeg, Canada (1983–1987)	RCT of doxycycline plus clindamycin vs doxycycline plus metronidazole (14 days)	Clinical examination; salpingitis confirmed by laparoscopy in 50 women	Interviews of women about intercourse without contraception and pregnancies; HSG performed on a few women	Follow-up: 5–7 months	0 of 10 women with *N. gonorrhoeae* PID had an adverse reproductive outcome, compared with 7 of 13 women with nongonococcal PID ($P = .007$), but only 3 of 7 infertile women had evidence of past or present CT (antibody or culture)	Laparoscopic confirmation of PID	Small sample size, small subgroup analyses, loss to follow-up, and short follow-up time for reproductive outcomes
Safrin et al [26] (1992)	51 of 140 women originally admitted for inpatient PID	San Francisco General Hospital (1985)	Retrospective cohort study	Hospital discharge diagnosis of PID, salpingitis, or tuboovarian abscess	Involuntary infertility (failure of conception after >1 year of unprotected intercourse); ectopic pregnancy; chronic pelvic pain (pelvic pain for >6 months); recurrent PID diagnosis	Telephone interview to assess long-term sequelae 3–4 years later	27% of 118 women *C. trachomatis* culture positive; among 51 women in retrospective cohort: involuntary infertility (40%), chronic pelvic pain (24%), recurrent PID (43%); ectopic pregnancy (2.4%); *C. trachomatis* did not significantly predict infertility in the entire cohort (data not reported); however, positive *C. trachomatis* culture result associated with involuntary infertility in women in whom index PID episode was the first (RR, 2.5; 95% CI, 1.0–6.2); *C. trachomatis* not associated with infertility among women with recurrent PID at admission ($P = .5$)	Lengthy follow-up	64% of patients could not be located and interviewed; small sample size; greater number of interviewed women had a tuboovarian abscess during index admission

Hillis et al [42] (1993)	443 women hospitalized for PID; included only those with cutures positive for *C. trachomatis* and/or *Neisseria gonorrhoeae* at time of PID (same population as [7])	University Hospital, Lund, Sweden (1960–1984)	Nested case-control study in prospective cohort of sequelae after PID	Clinically suspected by examination (not limited to those with laparoscopic confirmation)	76 case women with ectopic pregnancy or infertility (defined by failure to conceive despite regular unprotected intercourse for >1 year); 367 control women with intrauterine pregnancies; delayed care (seeking care for PID ⩾3 days after onset of lower abdominal pain)	4–14 years of follow-up	Overall, *C. trachomatis* monoinfection not more likely to be associated with impaired fertility than *N. gonorrhoeae* monoinfection or dual infection (OR, 0.9; 95% CI, 0.5–1.7); *C. trachomatis* associated with delayed care for PID (OR, 2.1; 95% CI, 1.0–4.1); delayed care associated with impaired fertility (OR, 2.6; 95% CI, 1.2–5.9); early treatment among women with *C. trachomatis* PID was strongly protective: 18 (18%) of 101 of those delaying care had impaired fertility compared to 0 (0%) of 13 of those seeking care promptly ($P<.05$); this effect was much less pronounced for *N. gonorrhoeae* infection	Large sample size; done within well-executed cohort with long follow-up	Results may not be generalizable to modern microbiologic and clinical setting; all women in the study had clinically suspected PID with *C. trachomatis* or *N. gonorrhoeae* infection; thus, relationship between *C. trachomatis* and impaired fertility biased to the null; however, suggests *C. trachomatis* PID no more or less likely to cause sequelae than *N. gonorrhoeae* PID
Haggerty et al [20] (2003)	614 women with clinically suspected PID recruited from ED, gynecology, STD clinics, and private practice (same population as [15])	13 US urban clinical sites (1996–1999)	Prospective cohort study	Clinically suspected by examination (all patients in cohort); endometrial biopsy with histology, *C. trachomatis* NAAT, and *N. gonorrhoeae* culture; endometritis (⩾5 neutrophils or ⩾2 plasma cells)	Pregnancy, infertility, chronic pelvic pain, and recurrent PID (see Ness et al [15])	2–5 years	Endometritis and/or endometrial infection with *C. trachomatis* or *N. gonorrhoeae* not associated with increased sequelae compared with clinically suspected PID without endometritis or endometrial infection; reduced pregnancy (OR, 0.8; 95% CI, 0.6–1.2); elevated infertility (OR, 1.0; 95% CI, 0.6–1.6); chronic pelvic pain (OR, 0.6; 95% CI, 0.4–0.9); recurrent PID (OR, 0.6; 95% CI, 0.4–0.9); 11 (19%) of 64 of those with endometrial *C. trachomatis* had infertility vs 81 (16.8%) of 523 of those without endometrial *C. trachomatis* (not significantly different); no differences for any other outcomes according to endometrial *C. trachomatis* result during baseline PID episode	Large sample size and lengthy follow-up; histologic confirmation of PID; modern-day assessment with active follow-up for outcomes of PID	All women had clinically suspected PID; thus, a true control group is lacking; endometritis may not always correlate with salpingitis

Haggerty et al [41] (2005)	780 women with clinically suspected PID, recruited from ED, gynecology, STD clinics, and private practice (same population as [15])	13 US urban clinical sites (1996–1999)	Prospective cohort study	Endometrial histology	Chronic pelvic pain, defined as pain reported at ⩾2 consecutive interviews conducted every 3–4 months	2–5 years	Endometritis or evidence of endometrial *Neisseria gonorrhoeae* or *C. trachomatis* infection was negatively associated with chronic pelvic pain (adjusted OR, 0.69; 95% CI, 0.44–1.10)	Large sample size and lengthy follow-up; histologic confirmation of PID; modern-day assessment with active follow-up for outcomes of PID	All women had clinically suspected PID; true control group lacking; those without *N. gonorrhoeae* or *C. trachomatis* may have been infected with other pathogens or had other conditions associated with chronic pain at baseline
Ness et al (4) (2008)	443 women with clinically suspected mild to moderate PID (same population as [15])	13 US urban clinical sites (1996–1999)	Prospective study	Clinical examination; serologic assessment: ELISA for antibodies to *C. trachomatis* EB and to Chsp60 at baseline and in final 2 years of follow-up	Times to pregnancy and recurrent PID	Mean of 84 months	Women whose anti-*C. trachomatis* EB antibodies in the final year of follow-up were in the highest tertile had: lower pregnancy rates (aHR, 0.47; 95% CI, 0.3–0.8), higher PID recurrence (aHR, 2.48; 95% CI, 1.0–6.3); baseline anti-*C. trachomatis* EB antibodies and antibodies to Chsp60 at either time point were not significantly associated with reproductive morbidity	Large sample size and serologic assessment of *C. trachomatis*, measuring cumulative exposure over a given time frame	Only half of the women enrolled in the parent study had sera available for analysis

NOTE. aHR, adjusted hazard ratio; Chsp60, *Chlamydia* heat shock protein 60; CI, confidence interval; EB, elementary bodies; ED, emergency department; ELISA, enzyme-linked immunosorbent serologic assay; HR, hazard ratio; HSG, hysterosalpingogram; NAAT, nucleic acid amplification test; RCT, randomized controlled trial; RR, relative risk; STD, sexually transmitted disease.

Table 4. Studies Assessing the Risk of Sequelae after at Least 1 Detected and Treated *Chlamydia trachomatis* Infection

Reference (year)	No. of women with treated *C. trachomatis* infection[a]	Population		Methods			Duration of follow-up	Incidence of PID	Validity
		Setting	Symptoms	Design	*C. trachomatis* test used	PID diagnosis			
Ness et al [44] (2006)	122	1170 women enrolled from family planning, university health and gynecology clinics, and STD units at 5 clinical US sites (1999–2001); predominately African-American women aged 13–36 years	Not specifically seeking care for an STD, but at elevated risk for chlamydial cervicitis, based on a scoring system; baseline *C. trachomatis* prevalence 10.2%	Prospective cohort study to assess risk factors for PID	Clinical examinations and *C. trachomatis* and *Neisseria gonorrhoeae* testing every 6–12 months; *C. trachomatis* test: NAAT	Criteria for PID on clinical examination or endometritis on endometrial biopsy (done if *C. trachomatis* or *N. gonorrhoeae* test positive at follow-up visit)	Median 3 years	Cumulative incidence of PID according to baseline *C. trachomatis* and *N. gonorrhoeae* results: *C. trachomatis* positive (18.8%), *N. gonorrhoeae* positive (18.8%), no infection (7.0%), overall (8.6%)	Large sample size, long follow-up, and active assessment for outcomes every 6–12 months were major strengths; study captured some cases of subclinical upper tract involvement, as women with a positive *N. gonorrhoeae* or *C. trachomatis* test results had endometrial biopsy; may not be generalizable, as limited to high-risk women receiving repeated 6–12 month *C. trachomatis* screening and timely treatment; cannot determine etiology of PID, when PID occurred, or whether an episode of PID is related to baseline *C. trachomatis* cervicitis
Low et al [43] (2006)	2965	Laboratory, hospital, and population registry data from all 43,715 women aged 15–24 years in Uppsala, Sweden (1985–1989); followed-up for outcomes through 1999	…	Retrospective population-based cohort study linking *C. trachomatis* test history and results with hospital codes	Culture (for most) and NAAT	Hospital diagnosis codes	10–14 years	Cumulative incidence of PID by age 35 years: *C. trachomatis* positive (5.6%), *C. trachomatis* negative (4.0%), not tested (2.9%), overall (3.9%); *C. trachomatis* positive vs. *C. trachomatis* negative: HR for PID, 1.5 (95% CI, 1.2–1.8), adjusted HR, 1.3 (95% CI, 1.0–1.6) controlling for demographic and socioeconomic factors	Large sample size; population-based; although some outpatient data captured, most were from inpatient records, thus limiting estimate to primarily severe PID; lowest PID rate in women never tested indicates preferential *C. trachomatis* testing among women at higher risk of PID; cannot determine etiology of PID, when PID occurred, or whether an episode of PID is related to a specific *C. trachomatis* infection; most cases of PID not preceded by a diagnosed *C. trachomatis* infection

NOTE. CI, confidence interval; ED, emergency department; EIA, enzyme immunoassay; HR, hazard ratio; NAAT, nucleic acid amplification test; PID, pelvic inflammatory disease; STD, sexually transmitted disease.

[a] Number of women with detected and treated *C. trachomatis* infection at baseline who were evaluated for PID at follow-up.

Table 5. Studies Assessing the Risk of Sequelae after Repeat *Chlamydia trachomatis* Infections

Reference (year)	Population	Setting	Study design	*C. trachomatis* and PID diagnosis	Outcomes	Time interval	Findings	Strengths	Limitations
Weström et al [7] (1992)	1844 women with laparoscopically confirmed salpingitis and 657 control women with clinically suspected PID but normal laparoscopy findings; inpatients	University Hospital, Lund, Sweden (1960–1984) (see Table 2)	Prospective cohort study	Laparoscopy	Infertility (failure to conceive despite regular unprotected intercourse for >1 year); tubal factor infertility verified by HSG, laparoscopy, laparotomy, or combination	Case and control women followed up for 13,400 and 3958 woman-years, respectively	Main results presented in Table 2; results related to repeat episodes of salpingitis; each case roughly doubled the risk of tubal factor infertility: after 1 episode salpingitis (8%), after 2 episodes salpingitis (19.5%), after 3 episodes salpingitis (40%)	Large sample size, laparoscopic confirmation of PID, and HSG identification of tubal factor infertility; control group	May not be generalizable to modern microbiological and clinical setting; assessed sequelae after repeat PID episodes, not after repeat *C. trachomatis* infection
Hillis et al [46] (1997)	11,000 women aged 10–44 years with at least one *C. trachomatis* infection; 644 with ⩾3 *C. trachomatis* infections, 2044 with 2 *C. trachomatis* infections, 8312 in random sample of women with 1 infection; *C. trachomatis* period prevalence 11% (family planning), 13% (STD clinics)	Family planning and STD clinics, Wisconsin (1985–1992)	Retrospective cohort study of number of *C. trachomatis* infections and subsequent PID or ectopic pregnancy hospitalizations, using linked registry data	Mostly culture; reported by public providers in Wisconsin *C. trachomatis* case registry	PID and ectopic pregnancy hospital discharge codes in statewide registry	7-year follow-up period	After adjustment, elevated risks of PID and ectopic pregnancy among women with more infections; PID: 1 infection (referent), 2 infections (OR, 4.0; 95% CI, 1.6–9.9), ⩾3 infections (OR, 6.4; 95% CI, 2.2–18.4); ectopic pregnancy: 1 pregnancy (referent), 2 pregnancies (OR, 2.1; 95% CI, 1.3–3.4), ⩾3 pregnancies (OR, 4.5; 95% CI, 1.8–5.3)	Population-based, cohort design	Unable to distinguish persistent vs new reinfection; no information on potential confounders; hospital discharge data may not be accurate and no outpatient data; clinicians may be more likely to diagnose PID in women with history of repeated *C. trachomatis* infections

Kimani et al [47] (1996)	302 urban female sex workers; mean age, 31 years; 54% HIV positive; 146 women had at least 1 *C. trachomatis* infection: 98 had uncomplicated cervical infection only, 23 had *C. trachomatis* PID, 25 had *C. trachomatis* and *Neisseria gonorrhoeae* infection	Special clinic in Nairobi, Kenya (1991)	Prospective cohort study evaluating risk factors for *C. trachomatis* PID vs uncomplicated *C. trachomatis* infection	EIA	Presence of new pelvic and adnexal tenderness on exam	Followed up for mean of 17.6 months	Independent risk factors for *C. trachomatis* PID included repeated *C. trachomatis* infection (adjusted OR, 1.8; 95% CI, 1.3–2.4; $P = .004$); women with *C. trachomatis* PID had more episodes of *C. trachomatis* infections ($P = .001$), but risk of PID per *C. trachomatis* infection among those with 1 infection (0.07 ± 0.26) was similar to that among women with repeated infections (0.13 ± 0.23; $P = .15$)	Prospective, well-done study showing multiple *C. trachomatis* infections associated with developing *C. trachomatis* PID rather than just *C. trachomatis* cervicitis	Small sample size in the *C. trachomatis* PID group, power limited to assess per infection risk; generalizability limited given high-risk Kenyan sex worker cohort
Ness et al [19] (2004)	684 women enrolled in RCT of inpatient vs outpatient treatment of mild to moderate PID; recruited from ED, gynecology, STD clinics, and private practice (same population as [15])	13 U.S. urban clinical sites (1996–1999)	Prospective study	Clinical examination	Patients interviewed every 3–4 months for outcomes of infertility (lack of pregnancy within 12 months among those reporting no effective contraception), chronic pelvic pain (consistent self-reports of pain of at least 6 months duration), recurrent PID (self-report)	Mean 35 months follow-up	Consistent condom use associated with lower risk for infertility (RR, 0.4; 95% CI, 0.2–0.9), chronic pelvic pain (RR, 0.7; 95% CI, 0.5–1.2), recurrent PID (RR, 0.5; 95% CI, 0.3–0.9)	Large sample size and lengthy follow-up; provides indirect evidence for association between repeat *C. trachomatis* and sequelae, as protective effect of condom use may be mediated by reduced exposure to *C. trachomatis*	Reliance on self-reported condom use may underestimate association

Bakken et al [45] (2007)	20,762 women born during 1970–1984 tested for *C. trachomatis;* 72,405 *C. trachomatis* tests done before first pregnancy; *C. trachomatis* period prevalence 18%	County in Norway (1990–2003)	Retrospective cohort study on number of *C. trachomatis* infections and subsequent ectopic pregnancy using linked registry data	~50% NAATs from 1 laboratory	Inpatient and outpatient ectopic pregnancy codes from county registry	…	Rate of ectopic pregnancy among those with pregnancies according to number of *C. trachomatis* infections: 0 infections (0.29 cases/PY; referent), 1 infection (0.58 cases/PY; aHR, 1.8 [95% CI, 1.1–3.0]), ⩾2 infections (1.39 cases/PY; aHR, 3.4 [95% CI, 1.5–8.0])	Population-based cohort design with good linkages, long follow-up, large sample size; use of inpatient and outpatient data	No information on potential confounders
Ness et al [4] (2008)	443 women with clinically suspected mild to moderate PID (same population as [15])	1996–1999	Prospective study	PID: clinical examination; serologic assessment: ELISA for antibodies to *C. trachomatis* EB and to Chsp60 at baseline and within final 2 years of follow-up	Times to pregnancy and recurrent PID	Mean of 84 months	Women whose anti–*C. trachomatis* EB antibodies in the final year of follow-up were in the highest tertile had: lower pregnancy rates (aHR, 0.47; 95% CI, 0.3–0.8), higher PID recurrence (aHR, 2.48; 95% CI, 1.0–6.3); baseline anti–*C. trachomatis* EB antibodies and antibodies to Chsp60 at either time point were not significantly associated with reproductive morbidity	Large sample size and *C. trachomatis* serologic assessment, measuring cumulative exposure over a given time frame; as later serology reflects baseline and subsequent *C. trachomatis* infections, findings suggest that additional *C. trachomatis* exposures after PID lead to greater risk of sequelae	Only half of the women enrolled in the parent study had serum samples available for analysis

NOTE. aHR, adjusted hazard ratio; Chsp60, *Chlamydia* heat shock protein 60; CI, confidence interval; EB, elementary bodies; ED, emergency department; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent serologic assay; HR, hazard ratio; HSG, hysterosalpingogram; NAAT, nucleic acid amplification test; OR, odds ratio; PID, pelvic inflammatory disease; PY, person-years; RCT, randomized controlled trial; RR, relative risk; STD, sexually transmitted disease.

women returning for a follow-up visit [34–36]. In a study in 2 Baltimore sexually transmitted diseases (STD) clinics, 3 (3%) of 93 women who tested positive for *C. trachomatis* by culture developed PID within a median of 2 weeks between testing and treatment [36]. Similarly, in a prospective STD clinic study involving 129 adults who tested positive for *C. trachomatis* by culture and nucleic acid amplification tests (NAATs), 2 women (2%) received a diagnosis of PID at a treatment visit that occurred a median of 13 days later [35]. Both of these women had ongoing chlamydial infection, and one had acquired a new gonococcal infection [35]. In a retrospective chart review study, Bachmann et al [34] also investigated the occurrence of PID during the period between testing and treatment in 67 mostly symptomatic women who tested positive for *C. trachomatis* in an emergency department or other high-risk clinical setting and reported that 3 (4.5%) of 67 women who did not receive therapy at the time of initial evaluation received a diagnosis of PID when they returned for treatment.

If the mean rate observed in this 2-week period (~3%) is assumed to be constant and to apply to all women with chlamydia, it would be expected that close to 18% of women would develop PID in 12 weeks, and >50% would develop PID in 1 year. However, 2 studies with longer follow-up periods did not report such high rates of PID (Table 1). The first, conducted in Sweden before the need to treat chlamydia was universally accepted, comprised 109 asymptomatic adolescent girls with untreated, culture-proven *C. trachomatis* infection, and 4 (3.7%) reported being hospitalized for salpingitis or seen in the emergency department for lower abdominal pain and vaginal discharge in the 3-month observation period [38]. In a more recent long-term follow-up study involving 30 healthy adult women who screened positive for *C. trachomatis* by NAAT, no women developed symptoms of chlamydial infection, none received *C. trachomatis*–specific antibiotic treatments, and none received a diagnosis of PID from her general practitioner or gynecologist within 1 year [37].

The highest estimate of PID after untreated chlamydial infection comes from a randomized trial in which 20 women coinfected with *C. trachomatis* and *N. gonorrhoeae* received adequate therapy for gonococcal but not chlamydial infection and were followed up for up to 7 weeks [39]. Six women (30%) received a diagnosis of PID from clinicians who were masked to the patients' chlamydial culture results.

Infertility and ectopic pregnancy after PID. Several studies have shown increased risks of reproductive and gynecologic sequelae after PID of any cause (Table 2) [7, 15, 27–29, 40]. Most notably, a landmark prospective study of 2501 Swedish women that was conducted by Weström et al [7] from the 1960s through the 1980s found that 16% of women with laparoscopically confirmed salpingitis developed infertility, compared with 2.7% of control women with clinically suspected PID who did not have salpingitis determined by laparoscopic examination. Infertility was defined by inability to conceive after 1 year of attempting to become pregnant. Tubal factor infertility was confirmed in 11.1% of cases and in none of the control women. In addition, among women with salpingitis, 9.1% of first pregnancies were ectopic pregnancies, compared with 1.4% of first pregnancies among control women. The severity of PID on laparoscopic examination affected long-term outcomes. Overall, 26% of women with clinically suspected PID had normal-appearing tubes on laparascopy; none of these women developed proven tubal factor infertility. Among women with a mild episode of salpingitis, only 0.6% developed tubal factor infertility, but 21% of those with a single episode of severe salpingitis had tubal factor infertility in ensuing years [7].

As part of a randomized controlled trial of treatment regimens for PID (the PID Evaluation and Clinical Health [PEACH] study), Ness et al [15] observed 831 women with mild to moderate clinically suspected PID for adverse outcomes during 1996–1999. Over a mean of 35 months of follow-up, 18% of the women reported infertility, 0.6% had an ectopic pregnancy, and 29% had some degree of chronic pelvic pain, with no differences by treatment arm. Among the 42% who became pregnant, the mean time to pregnancy was 21 months [15]. Laparoscopic verification of PID diagnoses, as done in the study by Weström et al [7], was not feasible in the PEACH study; however, endometrial biopsy was performed for a subset of 614 women [20, 41]. Rates of pregnancy, infertility, and chronic pelvic pain were not significantly different between women with and those without evidence of histologic endometritis [20, 41].

Some studies have also assessed the risk of infertility after PID that is specifically associated with *C. trachomatis* infection (Table 3) [2, 4, 20, 26, 41, 42]. In a retrospective cohort study involving 51 women hospitalized for PID in the 1980s, among women suffering their first episode of PID, those who were culture positive for *C. trachomatis* were more likely to experience involuntary infertility than were those who tested negative (relative risk, 2.5; 95% confidence interval [CI], 1.0–6.2) [26]. Furthermore, in a study involving women hospitalized during 1983–1987 for clinically suspected PID, 0 of 10 women with gonococcal PID experienced an adverse reproductive outcome, compared with 7 of 13 women with nongonococcal infection [2]. However, in a more recent study involving 614 women with clinically suspected PID, women with endometrial *C. trachomatis* infection had rates of subsequent infertility that were similar to those among women who did not have *C. trachomatis* detected in the endometrium (19% vs 16.8%) [20, 41]. In this study, endometritis and/or endometrial infection with *C. trachomatis* or *N. gonorrhoeae* was not associated with reduced pregnancy, elevated infertility, or increased chronic pel-

vic pain [20, 41]. The reasons for this are unclear. Antichlamydial and gonococcal PID treatment might have reduced the degree of damage preferentially in women with these infections (compared with other causes of clinically suspected PID), and endometritis does not always correlate with salpingitis [55–57]. In addition, women in all groups of this high-risk cohort may have had prior or subsequent *C. trachomatis* infection that resulted in tubal damage before or after the baseline PID episode, biasing results to the null. Indeed, a separate serologic investigation in this cohort revealed an association between *C. trachomatis* elementary body antibodies measured during the final year of follow-up and lower pregnancy rates [4].

The symptoms of PID may be less severe with *C. trachomatis* infection than with *N. gonorrhoeae* infection [58], which, in turn, may cause women to delay care for PID. In a nested case-control study in the cohort observed by Weström et al [7], among 76 case women who experienced infertility or ectopic pregnancy and 337 control women with a subsequent intrauterine pregnancy after PID, *C. trachomatis* was not associated with impaired fertility overall, compared with other causes of PID (odds ratio [OR], 0.9; 95% CI, 0.5–1.7) [42]. Although *C. trachomatis* infection was associated with delayed care (OR, 2.1; 95% CI, 1.0–4.1), which, in turn, was strongly associated with impaired fertility (adjusted OR, 2.8; 95% CI, 1.3–6.1), prompt treatment of chlamydia-associated PID dramatically lowered risk of sequelae much more so than did prompt treatment of gonococcal infection [42].

Summary. We found no prospective studies directly assessing risk of infertility after untreated *C. trachomatis* infection, and precise rates of progression are unknown. However, some data are available on risk of PID after untreated chlamydial infections and risk of infertility and other long-term outcomes after PID. The rate of PID after untreated *C. trachomatis* genital infection is challenging to determine accurately, because estimates vary widely across studies. In STD clinic or other high-risk populations in which untreated, detected chlamydial infection was followed up for ~2 weeks, rates of short-term PID diagnosis ranged from 2% to 4.5% [34–36]. If these rates were extrapolated to longer periods, we would expect a greater proportion of patients to develop PID. However, in a population of asymptomatic, untreated *C. trachomatis*–positive adolescent girls seeking birth control in Sweden, PID occurred in 3.7% over 12 weeks [38]. In the lowest-risk population evaluated thus far, Morré et al [37] observed no PID developing in 30 healthy adult women followed up for 1 year. All of these studies were relatively small and had limitations that could affect the accuracy of risk estimates. Nonetheless, differences in these results may be explained by several possible factors. First, PID rates may not be constant over time for several reasons. A disproportionate amount of PID might occur early in the course of chlamydial infection, when care-seeking in STD clinics or emergency departments is more likely because of recent high-risk behavior or symptoms. Host factors may contribute, with susceptible individuals developing tubal pathology early. Higher organism load may also play a role. In addition, immune responses developing over time could limit progression to the upper genital tract even when the infection is not resolved at the level of the cervix. Second, symptomatic infection prompting care-seeking may result in higher rates of PID than asymptomatic infection (eg, because of differences in host response). Third, there may be a lower threshold for PID diagnosis in high-risk settings or with a known untreated infection. Finally, PID rates may be higher in populations considered to be at high risk of sexually transmitted infections, because they may be more likely to have coinfections or bacterial vaginosis, have a history of PID, or experience recurrent infection [44]. Another factor that may influence differences among rates is the use of highly sensitive NAATs in some studies that may detect infections with a lower *C. trachomatis* burden and, perhaps, a lower likelihood for progression. The highest rates of PID were seen in the small ($n = 20$) but widely cited study by Stamm et al [39]. Coinfection with *N. gonorrhoeae* and a greater likelihood for recurrent chlamydial infection in this particularly high-risk population may explain the higher observed rate of sequelae.

After symptomatic PID has occurred, even with treatment, it is associated with significant reproductive and gynecologic morbidity, including infertility, ectopic pregnancy, and chronic pelvic pain [7, 15, 27–29, 40]. In the largest study of its kind, from the 1960s through the 1980s in Sweden, Weström et al [7] found that 16% of women with laparoscopically verified salpingitis developed infertility in the ensuing years, compared with 2.7% of control women with clinically suspected PID but no laparoscopic evidence of salpingitis. Ness et al [15] found that 18% of women developed infertility after clinically diagnosed PID during the 1990s in the United States, and the rate did not differ by presence or absence of histologic endometritis in a subsequent analysis by Haggerty et al [20]. In the study by Weström et al [7], severity of PID, as judged by laparoscopic examination, was associated with infertility, suggesting that tubal damage sustained at the time of acute PID may lead to sequelae [7, 29]. Among women with clinically suspected PID, none of those with normal-appearing tubes developed tubal factor infertility, whereas 21.4% of women with an episode of severe salpingitis did [7]. Although PID of any cause is strongly linked to sequelae [2, 4, 20, 26, 41, 42], data from the largest studies suggest that chlamydial PID is no more or less likely to lead to sequelae than other causes of PID [20, 41, 42].

When using PID as an intermediary outcome to estimate risk of long-term reproductive sequelae resulting from untreated *C. trachomatis* infection, it is important to understand the extent to which chlamydial infection may lead to these

sequelae outside the pathway involving symptomatic PID. Most women with tubal factor infertility and ectopic pregnancy have no history of diagnosed PID, including women in case-control studies showing strong associations between these outcomes and serologic evidence of past chlamydial infection [3, 5, 49]. However, in one study, further questioning of infertile women with no history of diagnosed PID revealed that 60% of those with tubal infertility reported health care visits for abdominal pain, compared with only 19% of those without tubal disease [59]. Nonetheless, it is known that chlamydial infection can cause asymptomatic or mildly symptomatic upper tract infection and inflammation [23, 25]. In addition, pathologic damage in fallopian tube biopsy specimens from women with tubal infertility is similar whether or not there is a history of overt PID [60]. Subclinical tubal infection and inflammation likely lead to some degree of infertility and other complications, but the full extent to which this occurs remains unclear.

Research needs and future directions. Quantifying the risks of PID, infertility, and ectopic pregnancy after untreated *C. trachomatis* infection would provide vital data for chlamydia control programs and for clinicians to share with patients on the importance of screening to prevent sequelae. To better understand the risk and timing of sequelae after untreated *C. trachomatis* infection, improvements must first be made in measuring the short-term complications of chlamydial infection. All of the studies reviewed in Table 1 followed up women for the development of clinically suspected PID and were therefore limited by the imprecise measurement of this outcome. The studies were also unable to capture cases of asymptomatic tubal inflammation and damage. As diagnostic misclassification compromises not only the estimation of PID after an untreated chlamydial infection but also sequelae after PID, it is of critical importance to develop standardized and innovative methods to ascertain both acute PID and subclinical tubal involvement associated with chlamydial infection. To increase sensitivity, the CDC recommends the minimum criteria for the diagnosis of clinically suspected PID as either uterine or adnexal tenderness or cervical motion tenderness [61]. However, this clinical approach, used by many studies to identify cases of PID, suffers from extremely poor specificity [17]. Laparoscopic examination or endometrial biopsies have been used by some studies to confirm PID, with laparoscopic examination considered to be the gold standard. However, neither of these confirmatory methods is very precise. Compared with laparoscopically diagnosed salpingitis, histologically confirmed endometritis has a sensitivity of 70%–89% and a specificity of 67%–92% [55–57]. Even laparoscopic examination has been found to have an extremely low sensitivity for the diagnosis of PID (25%–50%), when compared with fimbrial minibiopsy showing histopathologic evidence of PID [62, 63]. Furthermore, laparoscopic examination, which lacks standardization and relies on subjective interpretation of pelvic structure photographs, has only a fair intraobserver reproducibility for the diagnosis of PID ($\kappa = 0.58$) and a poor to fair interobserver reproducibility ($\kappa = 0.43$) [62].

In addition to concerns about its sensitivity and standardization, laparoscopic examination is an invasive procedure and is not routinely used in clinical practice. Noninvasive measures of PID are needed not only to be more clinically feasible but also to capture cases of subclinical tubal involvement in clinical studies. Magnetic resonance imaging (MRI) has been investigated as an alternative diagnostic procedure, although MRI facilities are not widely available at settings where patients with PID are typically seen. Data are limited, but those from at least 1 study ($n = 30$) suggest that MRI is sensitive (95%) and specific (89%) for the diagnosis of PID, compared with laparoscopic examination [64]. Transvaginal ultrasound is another minimally invasive procedure, but it has a much lower sensitivity for laparoscopically diagnosed PID (32%–81%) [64, 65]. Power Doppler, a recent innovation that allows improved detection of blood flow and inflammation-induced hyperemia, has been found in a study to have both high sensitivity (100%) and high specificity (80%), compared with laparoscopic examination [66]. Lastly, vaginal white blood cell count was found to be a sensitive marker of upper genital tract infection in a study involving 121 women meeting the CDC's minimal criteria for PID [67]. More work is needed to verify the diagnostic accuracy of these newer measures and additional inflammatory markers, such as interferon and other cytokines.

Next, to fully understand the natural history and sequelae of untreated chlamydial infection, we need additional prospective studies assessing rates of both clinically suspected PID and asymptomatic tubal inflammation after *C. trachomatis* infection in diverse populations encompassing the full spectrum of symptomatology and risk of sexually transmitted infection. Additional information on the 12-month incidence of PID after untreated *C. trachomatis* infection among asymptomatic college-aged women was recently collected as part of a randomized trial of chlamydia screening in the United Kingdom that was conducted before such screening was nationally recommended there [68, 69]. Although final results of the study were published too late for inclusion in this review, the natural history analysis revealed that 9.5% of 74 women with untreated chlamydial infection developed PID in 12 months [70]. Studying the timing of PID occurrence is also critical. The picture emerging from the studies listed in Table 1 suggests higher short-term rates of PID, with risk of PID decreasing after the first few weeks, and low rates within a year after asymptomatic infection. Understanding the timing of PID development is critical in optimizing the frequency and structure of chlamydial screening and other control strategies. Natural history studies are limited by the fact that it would be unethical to withhold treatment for diagnosed

chlamydial infection, and it is unclear how long a woman has already had infection at the time it is detected through testing. Nonetheless, creative strategies to develop prospective studies of chlamydia natural history are vital. Innovative use of stored genital specimens from existing or ongoing prospective studies of other infections (eg, human papillomavirus vaccine trials and human immunodeficiency virus prevention trials) in which specimens are collected beyond those used to diagnose and treat chlamydial infection as part of standard medical practice might also provide opportunities for better understanding of chlamydia natural history. Any study of *C. trachomatis* natural history would have to be carefully designed to ensure protection of human subjects. Finally, because of the challenges facing accurate diagnosis of PID and the occurrence of asymptomatic chlamydial upper tract involvement, as well as the difficulties in obtaining better natural history data, primary and secondary prevention strategies for *C. trachomatis* infection and its sequelae should be a focus of future studies, as discussed by Gottlieb et al in this supplement [71].

A primary necessity for research on sequelae after PID is identification of better, more proximal markers of tubal damage that are predictive of long-term sequelae. This would not only allow the outcomes of chlamydial infection to be more accurately classified but would also make prospective research on chlamydia and long-term outcomes more feasible. The landmark study by Weström et al [7] provided excellent data on risk of sequelae among women who were hospitalized with PID, compared with a control group of women with abdominal pain who did not have laparoscopically verified PID. However, these data were obtained in Sweden 20–40 years ago in a potentially much different microbiological and clinical milieu (eg, higher prevalence of *N. gonorrhoeae* and older PID treatment regimens). The PEACH study provided modern-day estimates of adverse outcomes after mild to moderate PID in the United States and stratified participants according to endometrial biopsy results but did not include a control group of women without clinically suspected PID [15]. Additional studies evaluating reproductive and gynecologic morbidity among women with PID, compared with an appropriate control group, in a modern-day setting would be valuable. In addition, prospective studies evaluating the risk of reproductive sequelae after subclinical upper genital tract infection and inflammation are needed. Preliminary data from a prospective study showed that 17% of 58 women with subclinical endometritis at a baseline visit had evidence of fallopian tube damage demonstrated by hysterosalpingogram 3 months later, whereas only 8% of 362 women without endometritis had such evidence [72]. Final results from this study have not yet been published. Finally, current evidence suggests that the vast majority of women infected with *C. trachomatis* do not develop PID, and not all women with chlamydial PID become infertile. Host factors and immunologic predictors explaining differences in morbidity risk should be explored in future studies, as discussed by Darville et al in this supplement [73]. Differences in morbidity after *C. trachomatis* infection may also be explained by simultaneous infection with other pathogens, such as *N. gonorrhoeae* [15] and *M. genitalium* [74], and the impact of such coinfection should be explored in future studies of PID and its sequelae.

Is the Risk of Sequelae Increased during a Repeat Chlamydial Infection?

PID after ⩾1 detected and treated chlamydial infection. A prospective assessment of PID after detected and treated *C. trachomatis* infection comes from a study of 1170 women from 5 US sites; all of the women were at high risk of chlamydia based on their demographic risk scores (Table 4) [44]. The women were tested for *C. trachomatis* and *N. gonorrhoeae* at baseline and were retested at follow-up visits every 6–12 months for a median of 3 years. Of these women, 122 tested positive for *C. trachomatis* at baseline and received antibiotic therapy. Twenty-three *C. trachomatis*–positive women (18.8%) received a diagnosis of PID (primarily mild to moderate) during follow-up. This rate of PID was substantially higher than that among women who did not have gonococcal or chlamydial cervicitis at baseline (7.0%). The etiology of subsequent PID episodes was unknown. The incidence of severe PID from any cause, stratified by *C. trachomatis* test history, was also assessed in a retrospective cohort study involving 43,715 Swedish women followed up from 1985 through 1999 [43]. Low et al [43] found that, by 15 years of follow-up, 6% of women had tested positive for *C. trachomatis* (and were assumed to have been treated), 4% of those who were screened and tested negative, and 3% of those never screened were subsequently treated for PID. Although some outpatient data were captured, most of the registry data were from inpatient records and, therefore, primarily measured the overall rate of severe PID. Women who tested positive for *C. trachomatis* were 50% more likely to be subsequently treated for PID than were women who tested negative (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.2–1.8), although this relationship was attenuated when adjusted for demographic and socioeconomic factors (HR, 1.3; 95% CI, 1.0–1.6) [43].

Repeat infections with *C. trachomatis* are common [33, 75, 76] and may contribute to the higher incidence of PID among women at high risk [39, 44], compared with women in the general population [37]. Similarly, the higher risk of repeat chlamydial infection among women with ⩾1 detected infection may help explain the higher rates of PID associated with longer follow-up of these women [43, 44].

PID after repeat chlamydial infection. The association between repeat infection and PID sequelae was assessed by a retrospective cohort study involving 11,000 women and girls

aged 10–44 years who tested positive for *C. trachomatis* in Wisconsin during 1985–1992 (Table 5) [46]. Women who tested positive twice were 4 times as likely (OR, 4.0; 95% CI, 1.6–9.9) and women who tested positive ⩾3 times were >6 times as likely (OR, 6.4; 95% CI, 2.2–18.4) to receive a diagnosis of PID [46]. It is difficult to determine the true impact of repeat chlamydial infection on PID from this study, however, because clinicians may be more likely to diagnose PID in women with a history of repeated chlamydial infection. Similarly, a prospective cohort study involving 302 urban female sex workers in Nairobi, Kenya, reported a significant relationship between repeated *C. trachomatis* isolation and the cumulative risk of chlamydial PID over ~18 months (adjusted OR, 1.8; 95% CI, 1.3–2.4) [47]. However, the risk of PID with each individual chlamydial infection appeared to be similar among those with one infection and repeated infections [47], although the power to detect a difference may have been limited. Thus, this study suggests that, although cumulative risk increases, the risk of PID per chlamydial infection may not be any greater with each recurrent episode. Although these studies were unable to distinguish between persistent and new repeat infection, they suggest that the risk of PID increases in parallel with the number of detected *C. trachomatis* infections.

Further demonstration of the relationship between recurrent chlamydial infection and risk of PID was evident in a prospective study involving 443 women with clinically suspected mild to moderate PID who were followed up for a mean of 84 months with repeated chlamydial serologic testing [4]. Although baseline antibodies to *C. trachomatis* elementary bodies were not associated with reproductive morbidity, rates of PID recurrence were higher among women whose anti-chlamydial antibodies were in the highest tertile during the final year of follow-up (adjusted HR, 2.5; 95% CI, 1.0–6.3). Later serologic testing, reflecting both baseline and subsequent chlamydial infections, was associated with PID recurrence, suggesting that additional exposures to *C. trachomatis* may increase the risk of subsequent PID [4]. Supporting this was the finding that consistent condom use in the same population was associated with a marked decrease in the incidence of recurrent PID [19].

Long-term reproductive sequelae after repeat chlamydial infection. In the same way that repeated chlamydial infection may increase the risk of PID, recurrent infection with *C. trachomatis* may also increase the risks of infertility and ectopic pregnancy. There is good evidence to suggest that recurrent PID increases sequelae risk, as first evidenced in the landmark Scandinavian cohort study involving 1844 women with laparoscopically confirmed salpingitis that was conducted by Weström et al [7]. In this study, each episode of salpingitis roughly doubled the risk of tubal factor infertility (8% after 1 episode, 20% after 2 episodes, and 40% after 3 episodes) [7]. Similarly, the studies by Ness et al [4, 19], in which higher titers of anti-chlamydial antibodies at follow-up and less consistent condom use were linked with recurrent PID, also showed that these factors were associated with longer times to pregnancy. These findings suggest that additional exposures to *C. trachomatis* after an episode of PID can lead to an increased risk of long-term complications.

In the retrospective cohort study assessing diagnosed chlamydia and sequelae risk that was conducted by Hillis et al [46], women who were identified as *C. trachomatis* positive 2 times in Wisconsin county databases from 1985 through 1992 were twice as likely (OR, 2.1; 95% CI, 1.3–3.4) and those with ⩾3 diagnosed infections were >4 times as likely (OR, 4.5; 95% CI, 1.8–5.3) to be hospitalized with an ectopic pregnancy. Another registry study involving 20,762 Norwegian women using the health care system from 1990 through 2003 reported a similar dose-response relationship between detected *C. trachomatis* infection and ectopic pregnancy [45]. Compared with women who tested negative for *C. trachomatis,* women with a history of a diagnosed chlamydial infection had almost a 2-fold increased risk of ectopic pregnancy (adjusted HR, 1.8; 95% CI, 1.1–3.0) and those with ⩾2 diagnosed chlamydial infections had a 3-fold increased risk of ectopic pregnancy (adjusted HR, 3.0; 95% CI, 1.6–5.6) [45].

Summary. Long-term follow-up studies of the period after treated chlamydial infection show that women with ⩾1 detected *C. trachomatis* infection have higher rates of PID in the ensuing years than do women without a detected infection, with PID rates near 20% over 3 years in a high-risk population [44]. Although a detected chlamydial infection may simply be a marker for high-risk sexual behavior and exposure to other sexually transmitted infections, one possible explanation for these findings is an increased risk of PID related to repeated *C. trachomatis* infections, which are common [75, 76].

Several studies have shown that the cumulative risk of PID [4, 46, 47] and long-term reproductive sequelae [4, 45, 46] increases with repeated chlamydial infections. However, it remains unclear from these epidemiologic studies whether the risk of sequelae from a given chlamydial infection is higher with each additional repeat infection. Furthermore, methodological problems make it difficult to sort out how much of the association between recurrent chlamydia and PID is attributable to biologically plausible mechanisms and how much is attributable to diagnostic ascertainment bias. Certainly, physicians' knowledge about prior positive chlamydial results may influence their differential diagnosis of lower abdominal pain. Because of the asymptomatic nature of chlamydial infection, it is also difficult to determine how many chlamydial infections a woman has actually had, if she did not seek medical care. Furthermore, it is difficult to determine whether a first diag-

nosed infection is truly primary and how many past infections have occurred when there is evidence of past infection. In all of these studies, infections were detected and therefore treated; however, perhaps the most enhanced pathologic memory immune response may occur after an initial infection that has resolved on its own. Lastly, the inability to distinguish between persistent and repeat infection limits interpretation.

Research needs and future directions. Studies on the natural history of repeated chlamydial infections are needed. Such studies should determine how the risk of PID in a given period after a repeat infection compares with the risk of PID in an equivalent period after an initial infection. In addition, because it is difficult to determine whether a woman's first diagnosed chlamydial infection is truly primary, natural history studies that conduct frequent *C. trachomatis* screenings and PID evaluations among a group of young, seronegative women are desirable. To conduct these natural history studies, a better understanding of chlamydia-associated antibodies would be valuable, in terms of the proportion of infections that result in seroconversion, the time course of seroconversion, duration of seroreactivity, and titers with initial and repeat infection. Furthermore, better markers of repeat infection and immunologic and host factors that predict worse tubal damage with repeat infection should also be explored [73]. Because of the high rates of PID from any cause in the years after a detected chlamydial infection in some populations [44], we also need studies of prevention strategies focused on women who have already received a diagnosis of at least one chlamydial infection. Recently, Ness et al [19] reported that consistent condom use was associated with a 30%–60% reduction in recurrent PID in a subgroup of 684 sexually active women followed up after an initial episode of PID. However, additional studies are needed to confirm these data and to determine optimal prevention strategies after diagnosed chlamydial infection in addition to those after PID.

CONCLUSION

Although the evidence linking *C. trachomatis* with tubal pathology is strong, there remains a great deal of uncertainty about the progression rates of both PID and reproductive sequelae among women acquiring *C. trachomatis* infection. Furthermore, the ability to link a specific chlamydial infection with later reproductive and gynecologic morbidity is limited. Prospective studies assessing the rates of symptomatic PID, asymptomatic tubal damage, and reproductive sequelae after *C. trachomatis* infection; better tools to measure PID and tubal damage; and studies on the natural history of repeated chlamydial infections are needed to better understand the long-term risks of chlamydial infection.

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